AHRQ Healthcare Horizon Scanning System – Potential High-Impact Interventions Report

Priority Area 11: Peptic Ulcer Disease and Dyspepsia

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Statement of Funding and Purpose

This report incorporates data collected during implementation of the Agency for Healthcare Research and Quality (AHRQ) Healthcare Horizon Scanning System by ECRI Institute under contract to AHRQ, Rockville, MD (Contract No. HHSA290-2010-00006-C). The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

This report's content should not be construed as either endorsements or rejections of specific interventions. As topics are entered into the System, individual topic profiles are developed for technologies and programs that appear to be close to diffusion into practice in the United States. Those reports are sent to various experts with clinical, health systems, health administration, and/or research backgrounds for comment and opinions about potential for impact. The comments and opinions received are then considered and synthesized by ECRI Institute to identify interventions that experts deemed, through the comment process, to have potential for high impact. Please see the methods section for more details about this process. This report is produced twice annually and topics included may change depending on expert comments received on interventions issued for comment during the preceding 6 months.

A representative from AHRQ served as a Contracting Officer's Technical Representative and provided input during the implementation of the horizon scanning system. AHRQ did not directly participate in horizon scanning, assessing the leads for topics, or providing opinions regarding potential impact of interventions.

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Financial Disclosure Statement

None of the individuals compiling this information has any affiliations or financial involvement that conflicts with the material presented in this report.

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Preface

The purpose of the AHRQ Healthcare Horizon Scanning System is to conduct horizon scanning of emerging health care technologies and innovations to better inform patient-centered outcomes research investments at AHRQ through the Effective Health Care Program. The Healthcare Horizon Scanning System provides AHRQ a systematic process to identify and monitor emerging technologies and innovations in health care and to create an inventory of interventions that have the highest potential for impact on clinical care, the health care system, patient outcomes, and costs. It will also be a tool for the public to identify and find information on new health care technologies and interventions. Any investigator or funder of research will be able to use the AHRQ Healthcare Horizon Scanning System to select potential topics for research.

The health care technologies and innovations of interest for horizon scanning are those that have yet to diffuse into or become part of established health care practice. These health care interventions are still in the early stages of development or adoption, except in the case of new applications of already-diffused technologies. Consistent with the definitions of health care interventions provided by the National Academy of Medicine (formerly the Institute of Medicine) and the Federal Coordinating Council for Comparative Effectiveness Research, AHRQ is interested in innovations in drugs and biologics, medical devices, screening and diagnostic tests, procedures, services and programs, and care delivery.

Horizon scanning involves two processes. The first is identifying and monitoring new and evolving health care interventions that are purported to or may hold potential to diagnose, treat, or otherwise manage a particular condition or to improve care delivery for a variety of conditions. The second is analyzing the relevant health care context in which these new and evolving interventions exist to understand their potential impact on clinical care, the health care system, patient outcomes, and costs. It is NOT the goal of the AHRQ Healthcare Horizon Scanning System to make predictions on the future use and costs of any health care technology. Rather, the reports will help to inform and guide the planning and prioritization of research resources.

We welcome comments on this Potential High-Impact Interventions report. Send comments by mail to the Task Order Officer named in this report to: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to: effectivehealthcare@ahrq.hhs.gov.

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Background

Horizon scanning is an activity undertaken to identify technological and system innovations that could have important impacts or bring about paradigm shifts. In the health care sector, horizon scanning pertains to identification of new (and new uses of existing) pharmaceuticals, medical devices, diagnostic tests and procedures, therapeutic interventions, rehabilitative interventions, behavioral health interventions, and public health and health promotion activities. In early 2010, the Agency for Healthcare Research and Quality (AHRQ) identified the need to establish a national Healthcare Horizon Scanning System to generate information to inform comparative-effectiveness research investments by AHRQ and other interested entities. AHRQ makes those investments in 14 priority areas. For purposes of horizon scanning, AHRQ's interests are broad and encompass drugs, devices, procedures, treatments, screening and diagnostics, therapeutics, surgery, programs, and care delivery innovations that address unmet needs. Thus, we refer to topics identified and tracked in the AHRQ Healthcare Horizon Scanning System generically as "interventions." The AHRQ Healthcare Horizon Scanning System implementation of a systematic horizon scanning protocol (developed between September 1 and November 30, 2010) began on December 1, 2010. The system is intended to identify interventions that purport to address an important unmet need, are up to 3 years out on the horizon, and if they have potential for high impact, to follow them up to 2 years after initial entry into the health care system. Since that implementation, review of more than 24,500 leads about potential topics has resulted in identification and tracking of about 2,400 topics across the 14 AHRQ priority areas and 1 cross-cutting area; about 750 topics are being actively tracked in the system at this time.

Methods

As part of the Healthcare Horizon Scanning System activity, a report on interventions deemed as having potential for high impact on some aspect of health care or the health care system (e.g., patient outcomes, utilization, infrastructure, costs) is aggregated semi-annually. Topics eligible for inclusion are those interventions expected to be within 0–3 years of potential diffusion (e.g., in phase III trials or for which some preliminary efficacy data in the target population are available) in the United States or that have just begun diffusing and that have completed an expert feedback loop.

The determination of impact is made using a systematic process that involves compiling information on topics and issuing topic drafts to a small group of various experts (selected topic by topic) to gather their opinions and impressions about potential impact. Those impressions are used to determine potential impact. Information is compiled for expert comment on topics at a granular level (i.e., similar drugs in the same class are read separately), and then topics in the same class of a device, drug, or biologic are aggregated for discussion and impact assessment at a class level for this report. The process uses a topic-specific structured form with text boxes for comments and a scoring system (1 minimal to 4 high) for potential impact in seven parameters. Participants are required to respond to all parameters.

The scores and opinions are then synthesized to discern those topics deemed by experts to have potential for high impact in one or more of the parameters. Experts are drawn from an expanding database ECRI Institute maintains of approximately 195 experts nationwide who were invited and agreed to participate. The experts comprise a range of generalists and specialists in the health care sector whose experience reflects clinical practice, clinical research, health care delivery, health business, health technology assessment, or health facility administration perspectives. Each expert

uses the structured form to also disclose any potential intellectual or financial conflicts of interest (COIs). Perspectives of an expert with a COI are balanced by perspectives of experts without COIs. No more than two experts with a possible COI are considered out of a total of the five to eight experts who are sought to provide comment for each topic. Experts are identified in the system by the perspective they bring (e.g., clinical, research, health systems, health business, health administration, health policy).

The topics included in this report had scores *and/or* supporting rationales at or above the overall average for all topics in this priority area that received comments by experts. Of key importance is that topic scores alone are not the sole criterion for inclusion—experts' rationales are the main drivers for the designation of potentially high impact. We then associated topics that emerged as having potentially high impact with a further subcategorization of "lower," "moderate," or "higher" within the high-impact-potential range. As the Healthcare Horizon Scanning System grows in number of topics on which expert opinions are received and as the development status of the interventions changes, the list of topics designated as having potentially high impact is expected to change over time. This report is being generated twice a year.

For additional details on methods, please refer to the full AHRQ Healthcare Horizon Scanning System Protocol and Operations Manual published on AHRQ's Effective Health Care Web site.

Results

The table below lists two topics for which (1) preliminary phase III data for drugs or phase II (or equivalent) data for devices and procedures were available; (2) information was compiled and sent for expert comment in this priority area; and (3) we received six to eight sets of comments from experts between January 1, 2015, and November 16, 2015. (Thirteen topics in this priority area were being tracked in the system as of November 6, 2015.) Both of these topics emerged as having potential for high impact on the basis of experts' comments; one was included in the previous potential high impact interventions report and the other is new in this report.

Readers are encouraged to read the detailed information on the intervention that follows the Executive Summary. The interventions are presented alphabetically.

Priority Area 11: Peptic Ulcer Disease and Dyspepsia

Topic	High-Impact Potential
1. Esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus	Moderately high
2. Rifaximin (Xifaxan) for treatment of diarrhea-predominant irritable bowel syndrome	Lower end of the high-impact-potential range; included in June 2015 potential high-impact interventions report

Discussion

Compared with other priority areas, we have identified relatively few leads and topics that meet inclusion criteria for new developments related to peptic ulcer and intestinal tract diseases in the horizon scanning system, despite extensive searches. Most research activity in this field focuses on drugs and biologics for irritable bowel syndrome and inflammatory bowel diseases (e.g., Crohn's disease, ulcerative colitis). We continue tracking novel drugs and interventions such as fecal microbiota therapy for ulcerative colitis that are in clinical trials but have not yet reported phase III data, and thus have not yet been sent to experts to obtain their comments.

Topics Deemed High-Impact

Cytosponge is a disposable esophageal cytology collection device for diagnosing and monitoring Barrett's esophagus, a potentially precancerous condition. It is of particular interest as clinicians seek less invasive, safe alternatives to diagnostic endoscopy procedures. Rifaximin is an antibiotic that acts in the gut for treating diarrhea-predominant irritable bowel syndrome.

Esophageal Cytology Collection System (Cytosponge) for Diagnosis of Barrett's Esophagus

- **Key Facts:** Esophageal cancer generally has a poor prognosis, with some studies reporting a 5-year survival rate of only 36% despite treatment. In the United States, the incidence today is nearly 3 times that of 30 years ago, rising from 3.6 cases per 1 million people in 1973 to 25.6 cases per 1 million people in 2006. This increase has raised interest in monitoring programs to detect Barrett's esophagus, a potentially precancerous condition, through endoscopic surveillance. However, universal screening with endoscopy is not recommended because most cases of Barrett's esophagus do not progress to esophageal cancer. The Cytosponge™ Cell Collection Device is intended to capture a sample of esophageal cells for laboratory analysis without the need for endoscopy, which is traditionally used to collect esophageal cells. The technology consists of a single-use, 30 mm spherical sponge compressed into a gelatin capsule and attached to a silicone-coated, braided polyester string. During a 10-minute procedure in a primary care provider's office, a patient swallows the capsule, and a nurse retrieves the expanded sponge shortly after applying a mild local anesthetic. Collected sponges are preserved and shipped to a laboratory for standard histological analysis. Based on results, physicians may recommend referral for additional endoscopic evaluation or periodic Cytosponge monitoring as part of an appropriate surveillance schedule to monitor changes in Barrett's esophagus.

  In July 2015, Ross-Innes and colleagues reported that Cytosponge cell collection combined with a biomarker for esophageal cancer may be more likely to detect early genetic changes linked to esophageal cancer than traditional endoscopic biopsy. Investigators noted that use of the Cytosponge, which samples cells along a much broader section of the esophagus, "may overcome sampling bias" and may provide more useful diagnostic information than traditional endoscopic biopsies that collect discrete tissue samples.

  The U.S. Food and Drug Administration (FDA) granted Covidien, plc (Dublin, Ireland), 510(k) clearance for the Cytosponge in November 2014, and although predicate devices were listed, one predicate is no longer marketed and the other is not designed to work like the Cytosponge. Costs for the Cytosponge device have not been widely reported yet. Clinical investigators at Cambridge University (United Kingdom) who evaluated the device estimated that Cytosponge testing would cost about £25 (US $36 as of November 16, 2015), which is roughly 4% of the cost of a traditional endoscopy evaluation for Barrett's esophagus. The single-use Cytosponge would also reduce or eliminate patients' potential exposure to pathogens from reusable endoscopes that may be inadequately cleaned.
- **Key Expert Comments:** Most experts thought this device's low cost and convenience for patients and providers have good potential to increase the number of patients monitored for Barrett's esophagus and potentially reduce the number of patients who present with advanced esophageal cancer. Clinical experts suggested the simple office-based test might encourage more primary care physicians to evaluate and monitor patients at increased risk of esophageal cancer and that its potential safety relative to endoscopy would be appealing. For

patients, a simple, 10-minute procedure that does not require sedation would likely be more acceptable and accessible than endoscopy and could encourage greater adherence to Barrett's esophagus monitoring protocols, experts thought.

- **High-Impact Potential:** Moderately high

Rifaximin (Xifaxan) for Treatment of Diarrhea-Predominant Irritable Bowel Syndrome

- **Key Facts:** Some researchers have hypothesized that the development of irritable bowel syndrome (IBS) symptoms, such as increased gas production, diarrhea, and weight loss, could be related to the microbiotic environment and bacterial overgrowth in the small intestine. Rifaximin is a nonsystemic, oral antibiotic derived from the antibiotic rifamycin that acts locally in the gut. It had been approved by FDA for treating travelers' diarrhea caused by *E. coli* in adults and children who are at least 12 years old and for treating hepatic encephalopathy in adults with liver failure. The drug was subsequently studied for its potential to reduce IBS symptoms, such as diarrhea. In May 2015, FDA approved rifaximin (Xifaxan®) 550 mg tablets for treating IBS with diarrhea in adults. For this indication, rifaximin's FDA-approved labeling recommends one 550 mg tablet, taken 3 times per day, for 14 days. According to labeling, patients who experience IBS recurrence can repeat the same treatment regimen up to two more times.

  In April 2015, Chey and colleagues reported that repeat rifaximin therapy was significantly more effective than placebo for reducing abdominal pain and improving stool consistency in 636 patients who had recurrent diarrhea-predominant IBS after responding to an initial 2-week course of rifaximin therapy. The rifaximin group had a significantly higher proportion of composite abdominal pain and stool consistency responders than the placebo group after the first repeat treatment (33% vs. 25%, $p=0.02$) and the second repeat treatment (35% vs. 27%, $p=0.03$). Patients in the rifaximin group also reported improvements of 8.1% to 9.2% in individual symptoms (abdominal pain, stool consistency, urgency, and bloating) compared with placebo after the first repeat treatment ($p<0.05$) and 7.6% to 12.1% after the second repeat treatment ($p<0.05$). The most common adverse events reported in both groups were nausea, upper respiratory tract infection, and urinary tract infection. As of November 2015, rifaximin costs shown on GoodRx, an aggregator of pharmacies' drug prices, are about $1,200 to $1,300 for 42 tablets at a dose of 550 mg each, which is enough for a recommended treatment course over 14 days. The drug is already widely available on third-party payer formularies, having been approved for other indications more than 5 years ago.
- **Key Expert Comments:** Experts generally thought that most physicians and patients would welcome the availability of a new oral drug to treat IBS, although some clinicians might be concerned about the potential for overprescribing antibiotics and an increase in microbial resistance. Although the drug may not provide effective relief of IBS in a large proportion of patients, it appears safe and effective for those patients whose symptoms respond to it. Most experts thought that the generally limited effectiveness of current IBS treatments creates an unmet need for new therapeutic options for patients with IBS. Some experts thought the drug might reduce some health disparities because it is indicated for use in men and women, unlike alosetron, which is approved to treat diarrhea-predominant IBS only in women.
- **High-Impact Potential:** Lower end of the high-impact-potential range

Peptic Ulcer Disease and Dyspepsia Interventions

Esophageal Cytology Collection System (Cytosponge) for Diagnosis of Barrett's Esophagus

Unmet need: Esophageal cancer generally has a poor prognosis, with some studies reporting a 5-year survival rate of only 36% after treatment with surgery alone or in combination with radiation or chemotherapy.[1] The incidence of esophageal cancer in the United States has substantially increased, from 3.6 cases per 1 million people in 1973 to 25.6 cases per 1 million people in 2006.[2] Similar large increases in esophageal cancer incidence have been reported in other Western countries in recent decades.[3] This increase has raised interest in monitoring programs to detect esophageal cancer through endoscopic surveillance.

A common surveillance strategy seeks to identify and monitor Barrett's esophagus, a potentially precancerous condition characterized by a change in esophageal cells that often occurs from chronic gastroesophageal reflux but typically produces no symptoms.[4] Endoscopic ablation using thermal or photochemical energy to eradicate abnormal cells in Barrett's esophagus may be effective for slowing or halting progression to esophageal cancer.[2,4] However, debate over esophageal cancer screening remains because no studies have demonstrated that screening decreases morbidity or mortality. Guidelines advise that monitoring should be limited to patients with increased cancer risk factors, including a history of symptomatic gastroesophageal reflux disease (GERD).[2,3] A technique for identifying Barrett's esophagus that improves patient comfort and lowers procedural costs compared with endoscopic surveillance could improve outcomes and monitoring cost effectiveness in patients at increased risk of esophageal cancer.

Intervention: The Cytosponge™ Cell Collection Device is intended to capture a sample of esophageal cells for laboratory analysis without the need for endoscopy, which is traditionally used to collect esophageal cells. The technology consists of a single-use, 30 mm spherical sponge compressed into a gelatin capsule and attached to a silicone-coated, braided polyester string.[5,6] To use the device, a patient swallows the capsule with water and loosely holds the string for about 5 minutes to allow the capsule to dissolve and the sponge to expand.[7] In clinical trials, a nurse sprayed the back of patients' throats with a 1% lidocaine solution before pulling the string and withdrawing the expanded mesh sponge. The extracted sponge is placed in preservative and kept at room temperature before transport to a clinical laboratory for standard pathological analysis. The entire Cytosponge procedure, including patient instruction, typically requires less than 10 minutes.[7]

Clinical trials: In January 2015, Ross-Innes and colleagues[8] reported positive results of Cytosponge testing in 1,042 patients at 11 hospitals in the United Kingdom. Subjects had either symptomatic gastroesophageal reflux (n=463) or confirmed diagnoses of Barrett's esophagus (n=647). Overall, 93.9% of patients successfully swallowed the Cytosponge. Using a visual analogue scale, patients rated the Cytosponge favorably compared with endoscopy ($p<0.001$). Patients who were not sedated for endoscopy were more likely to rate the Cytosponge higher than endoscopy (Mann-Whitney test, $p<0.001$). Cytosponge showed overall sensitivity of 79.9% (95% confidence interval [CI], 76.4% to 83.0%) that increased to 87.2% (95% CI, 83.0% to 90.6%) for patients with a circumferential area of Barrett's esophagus of 3 cm or more, a factor shown to increase esophageal cancer risk. Cytosponge sensitivity increased to 89.7% (95% CI, 82.3% to 94.8%) among 107 patients who swallowed the device twice during the study. Patients with dysplasia demonstrated no loss of sensitivity. Cytosponge had 92.4% specificity (95% CI, 89.5% to 94.7%) for ruling out Barrett's esophagus. Investigators identified no serious adverse events related to the Cytosponge procedure.[8]

In April 2015, Lao-Sirieix and colleagues[9] presented data from 73 patients being monitored for Barrett's esophagus. Patients underwent Cytosponge testing combined with immunohistochemical

staining for the biomarker trefoil factor 3 (TFF3) before planned endoscopic evaluation. Overall, 72 of 73 patients (98.6%) successfully swallowed the Cytosponge. One patient was willing to try again on a different day. Patients reported a median experience score of 8 (range, 6–10) for the Cytosponge on a 0–10 scale, with 10 indicating the best experience. One patient who underwent a planned endoscopic mucosal resection reported chest pain after the Cytosponge procedure and was admitted overnight. Another patient was found not to have Barrett's esophagus at endoscopy and was withdrawn from the study. Investigators detected abrasions in 95% of patients with 22.8% of patients experiencing oozing blood categorized as grade 3 or 4 (i.e., similar to that seen from an endoscopic biopsy site). The overall sensitivity of the combined Cytosponge-TFF3 test was 91.5% (65 of 71 were positive, 2 were negative due to inadequate sampling with no columnar cells, and 4 were TFF3 negative). When stratified for length of Barrett's esophagus tissue area, sensitivity increased from 90.1% for circumferential lengths of at least 1 cm to 91.7% for circumferential lengths of 3 cm.[9]

In July 2015, Ross-Innes and colleagues[10,11] reported that Cytosponge cell collection combined with the TFF3 biomarker may be more likely to detect early genetic changes linked to esophageal cancer than traditional endoscopic biopsy.[10,11] Researchers performed whole-genome sequencing on paired samples of Barrett's esophagus and esophageal adenocarcinoma (EAC) taken from 23 patients at a single time point and compared them to 73 samples taken from a single patient over 3 years. They found a wide range of cellular changes in Barrett's esophagus that may vary across areas sampled and "often shows surprisingly little overlap between EAC and adjacent Barrett's esophagus." However, investigators identified "a common causative insult underlying these two conditions."[10] Investigators noted that use of the Cytosponge may provide more useful diagnostic information than traditional endoscopic biopsies that collect discrete tissue samples. Ross-Innes and colleagues noted, "From a clinical perspective, the histopathological assessment of dysplasia appears to be a poor reflection of the molecular disarray within the Barrett's esophagus epithelium, and a molecular Cytosponge technique overcomes sampling bias and has the capacity to reflect the entire clonal architecture."[10]

Manufacturer and regulatory status: The U.S. Food and Drug Administration (FDA) granted Covidien, plc (Dublin, Ireland), 510(k) clearance for the Cytosponge in November 2014 before the company was acquired by Medtronic, plc (Dublin Ireland).[5,6] The Cytosponge premarket notification application cited its substantial equivalence to two predicate devices: the Cell-Mate Mass Cytology Cellular Retrieval System (510[k] cleared in 1993 but no longer marketed)[12] and an endoscopic cytology brush (U.S. Endoscopy Group, Inc., Mentor, OH).[13,14]

Diffusion: Covidien has not widely reported costs for the Cytosponge device. Clinical investigators at Cambridge University in the United Kingdom who evaluated the device estimated that Cytosponge testing would likely cost about £25 (US $36 as of November 16, 2015) compared with about £600 (US $925) for traditional endoscopic evaluation for Barrett's esophagus.[15-18]

The single-use Cytosponge to identify or periodically monitor Barrett's esophagus would be expected to reduce or eliminate patients' potential exposure to pathogens from reusable endoscopes that may be inadequately cleaned. Problems associated with inadequate cleaning and reprocessing of endoscopes have been recognized for several years, and FDA has published several safety advisories on these instruments.[19,20] In August 2015, Ofstead and colleagues at the Mayo Clinic (Rochester, MN), found that "despite reprocessing in accordance with US guidelines, viable microbes and biologic debris persisted on clinically used gastrointestinal endoscopes, suggesting current reprocessing guidelines are not sufficient to ensure successful decontamination."[21]

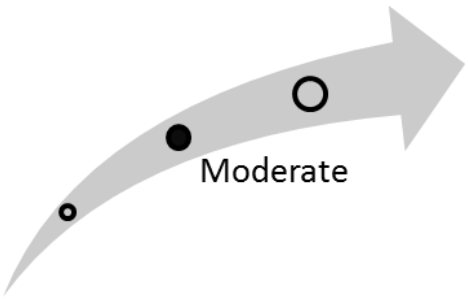
Besides the potential safety benefit from the disposable device, the Cytosponge's comparatively low cost relative to endoscopy would likely influence adoption and diffusion. In 2013, Benaglia and colleagues[22] developed a cost-effectiveness model to compare the health benefits and cost

effectiveness of screening for Barrett's esophagus using either the Cytosponge or conventional endoscopy versus no screening, and to estimate their abilities to reduce mortality from esophageal adenocarcinoma. Investigators estimated that in a cohort of 50-year-old men with symptomatic GERD, Cytosponge screening followed by treatment of dysplasia or intramucosal cancer would add $240 per screening participant (95% credible interval, $196 to $320) and produce a mean gain of 0.015 quality-adjusted life years (QALYs) with an incremental cost-effectiveness ratio of $15,700 per QALY. Screening endoscopy would add $299 per screening participant (95% credible interval, $261 to $367) and produce a mean gain of 0.013 QALYs with an incremental cost-effectiveness ratio of $22,200 per QALY. They estimated Cytosponge screening followed by treatment of patients with dysplasia or intramucosal cancer would reduce the number of cases of incident symptomatic esophageal adenocarcinoma by 19% compared with 17% for screening endoscopy, with the greater benefit due to more men accepting Cytosponge screening than endoscopic screening.[22]

Clinical Pathway at Point of This Intervention

Guidelines advise against screening for Barrett's esophagus in the general population. However, targeted endoscopic surveillance in patients with Barrett's esophagus and a history of symptomatic GERD to detect dysplasia and early cancer is the standard of care.[2,3,23] Endoscopic ablation using thermal or photochemical energy to eradicate abnormal cells in Barrett's esophagus may effectively slow or halt progression to esophageal cancer.[2,4] However, debate over esophageal cancer screening with endoscopy remains because most cases of Barrett's esophagus do not progress to esophageal cancer, and no studies have demonstrated that screening decreases morbidity or mortality. Cytosponge testing could be used in place of routine endoscopy for identifying and monitoring Barrett's esophagus, potentially improving patient comfort, lowering procedural costs, and identifying patients who may be indicated for additional endoscopic evaluation.

Figure 1. Overall high-impact potential: esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus



Most experts commenting on this intervention thought the Cytosponge system represents an important alternative to endoscopy for helping physicians identify and track Barrett's esophagus. Clinical experts were the most enthusiastic about the technology's potential to increase the number of patients in whom Barrett's esophagus is identified and monitored for changes suggestive of esophageal cancer development. Several experts suggested the technology's low cost and increased patient comfort combined with convenience for patients and clinicians relative to endoscopy could increase Barrett's esophagus identification and monitoring, potentially reducing the number of patients who present with advanced esophageal cancer when severe symptoms manifest. Based on this input, our overall assessment is that this intervention is in the moderate high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[24-29] We have organized the following discussion of expert comments by the parameters on which they commented. Note that some experts use the term "screening" interchangeably with "monitoring," although contextually they are referring to targeted followup or surveillance of patients at increased risk of having Barrett's esophagus, rather than true screening (universal testing of individuals without symptoms or an increased risk profile).

Unmet need and health outcomes: A majority of reviewers considered the availability of less-invasive and cheaper alternatives to endoscopy an important unmet need for monitoring patients with Barrett's esophagus.[24-26,28,29] However, the existence of endoscopy reduced the perceived unmet need of this population, one expert with a health systems background noted.[27] Two clinical experts saw the greatest unmet need. "We are likely underdiagnosing Barrett's esophagus. While we see many patients with GERD who have Barrett's esophagus, we also (unfortunately) often see patients presenting with esophageal cancer who have GERD [but] who never underwent prior endoscopy," one clinical expert noted, adding that "most patients with GERD likely never get a screening endoscopy."[24] The other clinical expert concurred, stating that "esophageal cancer is fatal if untreated, but if caught early, long term survival is possible. The problem is to identify patients who are at risk and put them into surveillance programs."[25] Both clinical experts cited cost and inconvenience of endoscopy as possible barriers to wider use of surveillance for Barrett's esophagus.[24,25] According to one clinical expert, another barrier may be "the over-the-counter availability of proton pump inhibitors, which allows self treatment."[24] Another clinical expert stated, "primary care doctors do not know when to refer patients for endoscopy or are not enthusiastic about setting up the screening."[25] This clinical expert surmised that use of Cytosponge, "would allow PCPs [primary care physicians] to keep the testing in their office and to be more liberal in screening. This would inevitably lead to an increase in screening, an increase in Barrett's [esophagus] being diagnosed, an increase in the number of patients getting screening, and by extension, a reduction in advanced cancers."[25] The other clinical expert agreed, noting the test could easily be done in a primary care office as soon as a patient reported GERD symptoms.[24] The Cytosponge's relative comfort and convenience compared with endoscopy could also encourage more patients who might benefit from Barrett's esophagus surveillance to continue with periodic monitoring, thought two experts with research backgrounds.[26,28]

Cytosponge has moderate to good potential to fill the unmet need for improved monitoring techniques for Barrett's esophagus, most experts thought. This sentiment was exemplified by one clinical expert's comment that "not enough patients are getting screened for Barrett's esophagus, and a lot of screened patients do not have it. This test will get more Barrett's esophagus patients into screening and avoid screening those who don't need it."[25] However, one expert with a health systems background doubted its potential, stating, "Although this intervention is quicker, more comfortable, and cheaper, it isn't a major leap in improving efficacy."[27]

Acceptance and adoption: All experts anticipated moderate to wide acceptance of Cytosponge testing from both health care providers and patients. For clinicians, the availability of additional data establishing the technology's noninferiority to traditional endoscopy would likely bolster acceptance, two research experts thought.[26,28] One clinical expert noted, "Of course, most people are averse to change. Since this changes the workflow, there would be resistance. On the other hand, most PCPs like to practice evidence-based medicine. So once there are published papers that validate the efficacy of this technology—and this information is readily available—they will eventually get on board."[25] One possible exception to overall clinician acceptance might come from endoscopists who might see fewer referrals if patients undergo the Cytosponge procedure in a

primary care provider's office, noted one research expert.[29] Another possible barrier to clinician acceptance is past experience with a related technology that "was a clinical success and a commercial failure a few years ago," according to one clinical expert.[24] "This [earlier device] was a variant on a capsule endoscope that was attached to a string, swallowed, took images of the distal esophagus to look for Barrett's esophagus, esophagitis, etc. That was a significantly more costly device, but it never took off clinically, and we still screen for Barrett's esophagus the same way now as we did before," this clinical expert stated.[24] Some published reports cite positive feedback from patients who underwent Cytosponge testing, and experts generally anticipate similarly positive feelings from patients in general clinical practice, especially as knowledge about the procedure spreads. According to one clinical expert, "The patients will be a little reluctant at first, but once it hits the popular press, and the patients realize how easy it is, they will get on board. (Not to mention encouragement from their PCP, whom they trust). This test will ultimately save more lives than cervical Pap smears. It is much less invasive. You don't even need to get undressed."[25]

Health care delivery infrastructure and patient management: Although the Cytosponge procedure would add work for primary care providers, experts did not expect these changes to be substantial. One research expert noted, "Patients that would ordinarily be sent for endoscopy could be managed in office, and the process of ongoing monitoring could be less burdensome."[28] Clinical experts suspected modest shifts in patient referral patterns. "Most patients with Barrett's esophagus are screened/surveilled by gastroenterologists. This device is geared for office use and could be used by family practice doctors, internists, and other primary care providers. I suspect this will actually help gastroenterologists by increasing the number of patients who actually need an endoscopy overall, but if implemented widely, this device could change the workflow and path to diagnosis for many patients," one clinical expert thought.[24] Another clinical expert noted, "there would be a mild disruption in a PCP office—someone needs to do the procedure and send the specimen off. However, this would probably be a reimbursed procedure. There are some [minor] storage issues, training, result tracking, and facility issues…[Cytosponge testing] would result in fewer screening EGDs [esophagogastroduodenoscopies] that turn up negative, but would probably increase the number of EGDs performed overall because of better identification of patients with Barrett's esophagus. This would be a mild increase that should be easily handled in existing GI [gastrointestinal] practices."[25] However, all experts suspected that prophylactic treatment of Barrett's esophagus to reduce cancer risk, if clinically indicated, would not change significantly whether patients were evaluated with Cytosponge or traditional endoscopy.

Health disparities: Experts generally agreed that the Cytosponge has some potential to reduce disparities because its low cost and ease of use relative to endoscopy could make it more accessible to patients of lower socioeconomic status in both rural and urban locales. Although access to any care might still present a barrier, these populations might have better access to a primary care provider, who could perform the test, than access to an endoscopist. One clinical expert noted, "In low income areas, where endoscopy may not be affordable for some, this may help to increase screening but a positive test will still warrant the more expensive and invasive endoscopy."[24] Another clinical expert surmised, "This intervention would be relatively low cost. It would eliminate some of the barriers—especially low socioeconomic status, language, and literacy. The patient gets the test done in a familiar location at low cost. If positive, it would be the necessary motivation for the PCP to get the patient to a gastroenterologist. Otherwise, the PCP makes a referral that may or may not be accomplished. The key here is that the patient has already breached the barriers by getting to the PCP's office. There would be no more health disparity barriers at that point to overcome when the Cytosponge is offered for screening."[25] The Cytosponge's convenience relative to endoscopy may also remove barriers for some patients, some experts suggested. One research expert noted, "as the procedure does not require sedation of the patient, individuals who

have limitations with respect to getting to and from healthcare centers and have difficulty scheduling procedures requiring sedation would also have improved access."[28]

Rifaximin (Xifaxan) for Treatment of Diarrhea-Predominant Irritable Bowel Syndrome

Unmet need: About 5% to 7% of U.S. adults have received a diagnosis of irritable bowel syndrome (IBS); however, some studies have estimated that up to 1 in 5 adults may be affected by the condition.[30] As many as 40% of these patients experience diarrhea-predominant IBS, characterized by symptoms including abdominal pain; loose, watery stools; and urgency.[31] No cure exists for IBS. Treatments are aimed at symptomatic relief, but questions of safety and efficacy remain. Only one medication, alosetron, has been approved by FDA for treating diarrhea-predominant IBS. However, alosetron has a labeled indication for use only in women. Further, alosetron is available only from physicians participating in a special manufacturer prescribing program and is associated with rare but serious side effects, including ischemic colitis and serious complications of constipation (mechanical or neuromuscular obstruction, impaction, toxic megacolon, secondary bowel ischemia, and perforation), that have resulted in hospitalization and, rarely, blood transfusion, surgery, and death.[32]

Intervention: Rifaximin is a nonsystemic, oral antibiotic that acts locally in the gut.[33] Researchers have hypothesized a relationship between gut microbiota and symptom development in patients with IBS. Bacterial overgrowth in the small intestine may lead to increased gas production, diarrhea, and weight loss.[30,34] Rifaximin is a semi-synthetic antibacterial agent derived from the antibiotic rifamycin SV, which purportedly inhibits bacterial RNA synthesis by binding to the beta subunit of bacterial DNA-dependent RNA polymerase. Rifaximin's antibacterial activity has the potential to reduce IBS symptoms, such as diarrhea.[33] When rifaximin is ingested, most of the antibiotic passes through the stomach and intestines and does not enter the bloodstream, thus limiting systemic antibiotic–associated side effects.[31,34] For treating IBS, rifaximin's labeled, recommended dosage is one 550 mg tablet, taken 3 times per day, for 14 days. Patients who experience IBS recurrence can repeat the same treatment regimen up to two more times.[34]

Clinical trials: In April 2015, Chey and colleagues[35] reported on efficacy of repeat rifaximin therapy in 636 patients who had recurrent diarrhea-predominant IBS within 18 weeks after responding to an initial 2-week course of rifaximin therapy. Subjects received two repeat courses of rifaximin or placebo. The primary endpoint was the proportion of treatment responders during at least 2 of the 4 weeks of followup. Treatment response was defined as a decrease in abdominal pain from baseline of 30% or more in mean weekly pain score and a decrease of 50% or more from baseline in number of days per week with loose or watery stool on the Bristol Stool Scale. Secondary endpoints included proportion of responders for individual symptoms: abdominal pain, stool consistency, urgency, and bloating. The rifaximin group (n=328) had a significantly higher proportion of composite abdominal pain and stool consistency responders than the placebo group (n=308) after the first repeat treatment (33% vs. 25%, p=0.02) and the second repeat treatment (35% vs. 27%, p=0.03). Patients in the rifaximin group also reported significant improvements of 8.1% to 9.2% in individual symptoms compared with placebo after the first repeat treatment ($p<0.05$) and 7.6% to 12.1% after the second repeat treatment ($p<0.05$). The most common adverse events were nausea (rifaximin group, 4%; placebo group, 2%), upper respiratory tract infection (rifaximin group, 4%; placebo group, 3%), and urinary tract infection (rifaximin group, 3%; placebo group, 5%).[35]

In April 2015, Pimental and associates[36] reported treatment-response results from its TARGET-3 study of 2,579 patients who received rifaximin to treat diarrhea-predominant IBS. After the initial 2-week rifaximin regimen, 42% of patients (1,074 of 2,579) were deemed treatment responders, defined as having reductions of at least 30% in pain and at least 50% in number of days experiencing loose or watery stools (the primary endpoint). Among initial treatment responders,

36% did not have recurrent diarrhea-predominant IBS symptoms; however, the remainder (64% [692 of 1,074]) of initial responders had relapsed disease at up to 18 weeks of followup. Investigators randomly assigned 636 initial responders with recurrent IBS to receive a repeat course of rifaximin or placebo. Repeat treatment achieved the primary endpoint in 33% of the rifaximin group and 25% of the placebo group (p=0.02). An additional repeat course of rifaximin or placebo achieved the primary endpoint in 37% of the rifaximin group and 29% of the placebo group (p=0.04). Adverse-event rates were similar and were reported in 43% of rifaximin patients and 46% of placebo patients.[36]

Manufacturer and regulatory status: Salix Pharmaceuticals, Inc. (Morrisville, NC), a subsidiary of Valeant Pharmaceuticals International, Inc. (Laval, Quebec, Canada), developed rifaximin for treating diarrhea-predominant IBS.

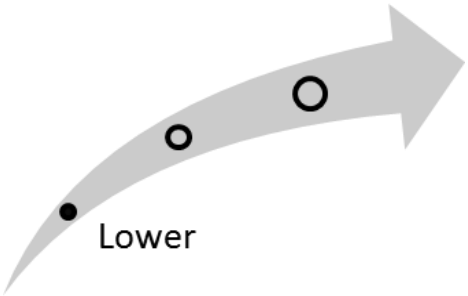
In May 2015, FDA approved rifaximin 550 mg tablets with the trade name Xifaxan® under a supplemental new drug application for treating IBS with diarrhea in adults.[31,37] Per approved labeling, rifaximin dosage for treating IBS is 550 mg, 3 times per day, for 14 days. In patients with recurrent IBS with diarrhea, a course of rifaximin can be repeated up to twice at the same dosage.[34] In 2 earlier approvals, FDA approved rifaximin tablets in May 2004 for treating *E. coli*-related diarrhea in adults and children aged 12 years or older, at a dosage of 200 mg, 3 times per day, for 3 days. In March 2010, FDA approved the drug for reducing the "risk of overt hepatic encephalopathy recurrence in adults" at a dosage of 550 mg tablets twice per day.[34,38]

Diffusion: As of November 2015, Valeant reported "strong Xifaxan script uptake" after its approval for treating diarrhea-predominant IBS, without specifying sales figures or projections for the drug.[39] Rifaximin 550 mg tablets have been commercially available in the United States since March 2010, indicated for reducing the risk of overt hepatic encephalopathy recurrence in adults. As of November 2015, rifaximin reportedly costs about $1,200 to $1,300 for 42 pills (i.e., 550 mg taken 3 times per day for 14 days).[40] The manufacturer offers copayment assistance for some insured or uninsured patients who meet eligibility requirements.[41] The drug is widely available on third-party payer formularies, having been approved more than 5 years ago for the other indications.

Clinical Pathway at Point of This Intervention

Treatment for IBS focuses on responding to symptoms through changes in diet and lifestyle, improvement of gastrointestinal health (e.g., using laxatives or antidiarrheals as appropriate), and use of stress-relief techniques and psychotherapy.[30,42-45] Before rifaximin's May 2015 approval, FDA had approved only one drug, alosetron, for treating diarrhea-predominant IBS, and it is approved for use only in women. Rifaximin will be used as a primary pharmacotherapy for patients with diarrhea-predominant IBS who have not obtained adequate relief from conservative measures, such as diet and stress relief techniques.

Figure 2. Overall high-impact potential: rifaximin (Xifaxan) for treatment of diarrhea-predominant irritable bowel syndrome



Most experts who commented on this intervention noted the need for more effective treatments for diarrhea-predominant IBS, with clinical experts rating the unmet need as higher than other experts. Experts noted that although the treatment may not provide adequate relief in about half of patients who initially try it, patients who do respond generally appear to do well, and up to two repeat treatments may ultimately provide relief. Several experts thought many clinicians and patients would welcome another drug approved to treat IBS, given the limited availability of drugs with labeled indications for treating diarrhea-predominant IBS. Some experts believe that concerns about overuse of antibiotics might limit the use of the drug. However, other experts thought the availability of a new IBS therapy with a seemingly good safety profile would be appealing to many clinicians and their patients. Based on this input, our overall assessment is that this intervention is in the lower end of the high-impact-potential range.

Results and Discussion of Comments

Six experts, with clinical, research, and health systems backgrounds, offered comments on this intervention.[46-51] We have organized the following discussion of expert comments by the parameters on which they commented. The experts made their comments before rifaximin's May 2015 approval as an IBS treatment.

Unmet need and health outcomes: Five experts with clinical and research backgrounds rated the unmet need for effective new IBS treatments as moderate to high,[46-49,51] with clinical experts rating the unmet need highest.[46,49] "Irritable bowel syndrome is a chronic condition that accounts for millions of health care visits and millions in dollars in health care costs annually," one clinical expert noted, adding that "symptoms can be quite burdensome to patients and thus as a result of very limited therapeutic options, alternative therapies are needed. An effective therapy has the potential to improve the associated morbidity of irritable bowel syndrome and improve the quality of life of patients."[49] A health systems expert countered, "Ultimately, irritable bowel syndrome affects a small number of individuals in the United States. While there is only said to be one medication approved by the FDA to treat irritable bowel syndrome with diarrhea, it appears as though there are multiple off-label treatment methods used to treat patients with this disorder. For this reason, treating irritable bowel syndrome appears to only have minimal importance."[50]

Experts were divided on rifaximin's potential to improve health outcomes and fulfill the unmet need for effective new treatments for diarrhea-predominant IBS. One health systems expert noted: "In general, it appears as though Xifaxan has the potential to effectively treat irritable bowel syndrome, according to the clinical studies. However, the variety of other off label options creates a competition for use. Overall, there is only a minimal potential for Xifaxan to fulfill the unmet need."[50] However, one clinical expert stated, "This is a relatively unappreciated and unused modality in family practice, internal medicine, and gastroenterology practices. It has the potential to

improve the lifestyle of millions of patients (e.g., not being tethered to a bathroom, able to work, etc.). Expanded use of this intervention would have a huge impact on quality of life and productivity."[46] This clinical expert added, "The majority of patients with irritable bowel syndrome are not satisfied with their treatment efficacy. This intervention would reduce the percentage of those patients…. It does not work in everyone, but when it does work, it is impressive."[46] One research expert presented a middle ground, stating, "The treatment sounds promising, but there are still questions about how frequently a patient would need to be treated for this disabling condition. Since current treatments can be associated with significant adverse effects and rifaximin does not seem to have this concern, it could meet an unmet need."[47]

Acceptance and adoption: Most experts anticipated good acceptance for rifaximin from both physicians and patients with IBS.[46-49,51] One clinical expert noted, "Doctors would love it - an oral pill to treat irritable bowel syndrome that works with minimal or no side effects. Perfect," and that "Patients would love it - an oral pill to treat irritable bowel syndrome that works with minimal or no side effects. Almost perfect - it is not a one-shot cure. THAT would be perfect."[46] However, one health systems expert thought that "it appears as though Xifaxan has the potential to effectively improve the condition of a patient with irritable bowel syndrome. However, there are multiple other treatment options, even if many of them are considered off label. For this reason, it is likely that clinicians will minimally accept the use of Xifaxan to treat irritable bowel syndrome."[50] One clinical expert who expected good physician acceptance also observed that some "clinicians may be apprehensive about utilizing antibiotics at increasing rates due to concerns about antibiotic resistance."[49]

Health care delivery infrastructure and patient management: Most experts believe that the availability of rifaximin as an oral drug to treat IBS would likely cause little disruption to health care infrastructure or the way physicians manage patients with IBS.[47-51] However, one clinical expert thought that rifaximin might disrupt both health care infrastructure and patient management. The clinical expert stated, "The disruption would be a good one. Fewer office visits for irritable bowel syndrome symptoms and exacerbations would be needed. There would be fewer referrals from primary care offices to specialists. There would be fewer hospitalizations."[46] This clinical expert stated that for patient management, "the disruption would be moderate, depending on the number of irritable bowel syndrome patients in the practice and the efficacy of the intervention. For example, in practices with 20% irritable bowel syndrome prevalence (not uncommon), if 30% of patients are improved on rifaximin, then that could be an effect on 6% of the practice's patient population. That is not an insignificant number."[46]

Health disparities: Two experts thought rifaximin might help alleviate gender-based disparities, because the only other FDA-approved drug for treating diarrhea-predominant IBS, alosetron, is indicated for use only in women.[49,51] Looking at this issue from another angle, one clinical expert noted, "IBS tends to impact women more than men. Given this gender disparity, this therapy has the potential to diminish gender-specific disparities in this chronic condition."[49] Other experts doubted whether the drug would substantially impact health disparities, although the potential to increase disparities exists if patients face barriers to insurance coverage for rifaximin. One clinical expert noted, "This is an expensive medication if not covered by the patient's formulary - if they have insurance at all. Since they would not have the benefit of the medication, they would be sicker and more prone to losing days at work and in caring for their families. Disability due to irritable bowel syndrome is not the norm, but it does occur in some cases. The lack of access to this intervention would make disability more likely, again in lower socioeconomic status groups."[46]

References

1. Reynolds JV, McGillycuddy E, Ravi N, et al. Modern oncologic and operative outcomes for oesophageal cancer treated with curative intent. Ir Med J. 2011 Sep;104(8):235-8. PMID: 22125876.
2. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. JAMA. 2013 Aug 14;310(6):627-36. PMID: 23942681.
3. de Jonge PJ, van Blankenstein M, Grady WM, et al. Barrett's oesophagus: epidemiology, cancer risk and implications for management. Gut. 2014 Jan;63(1):191-202. Also available: http://dx.doi.org/10.1136/gutjnl-2013-305490. PMID: 24092861.
4. Old OJ, Almond LM, Barr H. Barrett's oesophagus: how should we manage it? Frontline Gastroenterol. 2015;6:108-16. Also available: http://fg.bmj.com/content/6/2/108.abstract.
5. Indications for use. Cytosponge cell collection device. K142695. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2014 Nov 19. 2 p. Also available: http://www.accessdata.fda.gov/cdrh_docs/pdf14/K142695.pdf.
6. Covidien, LLC. 510(k) summary for Cytosponge cell collection device. K142695. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2014 Nov 19. 3 p. Also available: http://www.accessdata.fda.gov/cdrh_docs/pdf14/K142695.pdf.
7. Kadri SR, Lao-Sirieix P, O'Donovan M, et al. Acceptability and accuracy of a non-endoscopic screening test for Barrett's oesophagus in primary care: cohort study. BMJ. 2010;341:c4372. Also available: http://www.bmj.com/content/341/bmj.c4372. PMID: 20833740.
8. Ross-Innes CS, Debiram-Beecham I, O'Donovan M, et al. Evaluation of a minimally invasive cell sampling device coupled with assessment of trefoil factor 3 expression for diagnosing Barrett's esophagus: a multi-center case-control study. PLoS Med. 2015 Jan 1;12(1):1-19. Also available: http://dx.doi.org/10.1371/journal.pmed.1001780.
9. Lao-Sirieix P, Debiram-Beecham I, Kerr S, et al. Evaluation of a minimally-invasive cytosponge esophageal cell collection system in patients with barrett's esophagus. Gastroenterol. 2015 Apr;148(4):S-16. Also available: http://www.sciencedirect.com/science/article/pii/S0016508515300548.
10. Ross-Innes CS, Becq J, Warren A, et al. Whole-genome sequencing provides new insights into the clonal architecture of Barrett's esophagus and esophageal adenocarcinoma. Nat Genet. 2015 Sep;47(9):1038-46. Epub 2015 Jul 20. Also available: http://dx.doi.org/10.1038/ng.3357. PMID: 26192915.
11. ˜Pill on a string' could help spot early signs of cancer of the gullet. [internet]. Cambridge (UK): University of Cambridge; 2015 Jul 20 [accessed 2015 Sep 10]. [7 p]. Available: http://www.cam.ac.uk/research/news/pill-on-a-string-could-help-spot-early-signs-of-cancer-of-the-gullet.
12. 510(k) premarket notification. Cell-Mate mass cytology-cellular retrieval sysemt. K934193. [internet]. Silver Spring (MD): U.S. Food and Drug Administration; 1993 Nov 19 [accessed 2015 Sep 11]. [2 p]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K934193.
13. US Endoscopy. Indications for use. Cytology brush. K103437. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 1 p. Also available: http://www.accessdata.fda.gov/cdrh_docs/pdf10/K103437.pdf.
14. 510(k) premarket notification. Cytology Brush. K924104. [internet]. Silver Spring (MD): U.S. Food and Drug Administration; 1992 Nov 24 [accessed 2015 Sep 11]. [2 p]. Available: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K924104.
15. XE currency converter. [internet]. Newmarket (ON): XE.com [accessed 2015 May 01]. [2 p]. Available: http://www.xe.com/currencyconverter/.
16. Van Marsh A. Sponge test a low-cost, easier way to spot signs of cancer. [internet]. New York (NY): CBS News; 2014 Nov 21 [accessed 2015 Sep 11]. [4 p]. Available: http://www.cbsnews.com/news/sponge-test-a-low-cost-accurate-way-to-spot-signs-of-cancer/.

17. Roberts M. 'Sponge' test for gullet cancer looks promising. [internet]. London (UK): BBC News; 2014 Nov 4 [accessed 2015 Sep 11]. [8 p]. Available: http://www.bbc.com/news/health-29877701.

18. Gaffey C. 'Pill on a string' could speed up cancer diagnoses and save thousands of lives. [internet]. New York (NY): Newsweek LLC; 2015 Jul 20 [accessed 2015 Sep 11]. [2 p]. Available: http://www.newsweek.com/pill-string-could-save-thousands-lives-early-cancer-diagnosis-355698.

19. Infections associated with reprocessed duodenoscopes. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 Aug 17 [accessed 2015 Sep 15]. [7 p]. Available: http://www.fda.gov/medicaldevices/productsandmedicalprocedures/reprocessingofreusablemedicaldevices/ucm454630.htm.

20. Rudy SF, Adams J, Waddington C. Implementing the SOHN-endorsed AORN guidelines for reprocessing reusable upper airway endoscopes. ORL Head Neck Nurs. 2012 Dec;30(1):6-15. PMID: 22474919.

21. Ofstead CL, Wetzler HP, Doyle EM, et al. Persistent contamination on colonoscopes and gastroscopes detected by biologic cultures and rapid indicators despite reprocessing performed in accordance with guidelines. Am J Infect Control. 2015 Aug 1;43(8):794-801. Also available: http://dx.doi.org/10.1016/j.ajic.2015.03.003. PMID: 26234219.

22. Benaglia T, Sharples LD, Fitzgerald RC, et al. Health benefits and cost effectiveness of endoscopic and nonendoscopic cytosponge screening for Barrett's esophagus. Gastroenterology. 2013 Jan;144(1):62-73.e6. Also available: http://dx.doi.org/10.1053/j.gastro.2012.09.060. PMID: 23041329.

23. Whiteman DC, Appleyard M, Bahin FF, et al. Australian clinical practice guidelines for the diagnosis and management of Barrett's Esophagus and Early Esophageal Adenocarcinoma. J Gastroenterol Hepatol. 2015 May;30(5):804-20. Epub 2015 Jan 22. Also available: http://dx.doi.org/10.1111/jgh.12913. PMID: 25612140.

24. Expert Commenter 25. (External, Clinical). Horizon Scanning Structured Comment Form. HS2396 - Esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus. 2015 Oct 8 [review date].

25. Expert Commenter 343. (External, Clinical). Horizon Scanning Structured Comment Form. HS2396 - Esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus. 2015 Oct 12 [review date].

26. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2396 - Esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus. 2015 Oct 22 [review date].

27. Expert Commenter 1015. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS2396 - Esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus. 2015 Oct 15 [review date].

28. Expert Commenter 1321. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS2396 - Esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus. 2015 Oct 14 [review date].

29. Expert Commenter 1384. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS2396 - Esophageal cytology collection system (Cytosponge) for diagnosis of Barrett's esophagus. 2015 Oct 19 [review date].

30. National Digestive Diseases Information Clearinghouse (NDDIC). Irritable bowel syndrome. [internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); 2013 Sep 01 [accessed 2014 Sep 26]. [12 p]. Available: http://www.digestive.niddk.nih.gov/ddiseases/pubs/ibs/ibs_508.pdf.

31. Salix announces FDA approval of Xifaxan 550 mg for the treatment of IBS-D (irritable bowel syndrome with diarrhea). [internet]. Laval (Quebec): Valeant Pharmaceuticals International, Inc.; 2015 May 27 [accessed 2015 Jun 03]. [3 p]. Available: http://ir.valeant.com/investor-relations/news-releases/news-release-details/2015/Salix-Announces-FDA-Approval-of-Xifaxan-550-mg-for-the-Treatment-of-IBS-D-Irritable-Bowel-Syndrome-with-Diarrhea/default.aspx.

32. Highlights of prescribing information: Lotronex (alosetron hydrochloride) tablets. San Diego (CA): Prometheus Laboratories, Inc.; 2014 Mar. 27 p. Also available: https://www.lotronex.com/Documents/Lotronex_PI.pdf.

33. Xifaxan (rifaximin) tablets. Raleigh (NC): Salix Pharmaceuticals, Inc.; 2014 Mar. 19 p.

34. Salix Pharmaceuticals, Inc. Highlights of prescribing information: Xifaxan (rifaximin) tablets, for oral use. Raliegh (NC): Salix Pharmaceuticals, Inc.; 2015 May. 7 p. Also available: https://shared.salix.com/shared/pi/xifaxan-pi.pdf.

35. Chey WD, Chang L, Lembo A, et al. Effects of rifaximin on urgency, bloating, and abdominal pain in patients with IBS-D: a randomized, controlled, repeat treatment study. Gastroenterology. 2015 Apr;148(4):1. Also available: http://www.sciencedirect.com/science/article/pii/S0016508515302420.

36. Pimental M, Chang L, Lembo A, et al. Mo1279 durability of benefit in IBS-D patients responding to a 2-week course of rifaximin: results from TARGET 3. Gastroenterology. 2015 Apr;148(4):S658-9. Also available: http://www.gastrojournal.org/article/S0016-5085(15)32224-1/pdf.

37. FDA approves two therapies to treat IBS-D. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 May 27 [accessed 2015 Jun 03]. [5 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm448328.htm.

38. FDA approves new use of Xifaxan for patients with liver disease. [internet]. Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2015 Mar 24 [accessed 2015 Nov 20]. [2 p]. Available: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm206104.htm.

39. Valeant Pharmaceuticals reports third quarter 2015 financial results. [internet]. Laval (QB): Valeant Pharmaceuticals; 2015 Oct 19 [accessed 2015 Nov 17]. [12 p]. Available: http://ir.valeant.com/investor-relations/news-releases/news-release-details/2015/Valeant-Pharmaceuticals-Reports-Third-Quarter-2015-Financial-Results/default.aspx.

40. Xifaxan pricing info. [internet]. Santa Monica (CA): GoodRx, Inc. [accessed 2015 Nov 17]. [9 p]. Available: http://www.goodrx.com/xifaxan?form=tablet&dosage=550mg&quantity=42&label_override=Xifaxan.

41. Instant savings card. Raleigh (NC): Salix Pharmaceuticals; 1 p. Also available: https://www.xifaxan.com/DesktopModules/CopayCard/xifaxanPDF/59984859508.pdf.

42. Mayo Clinic staff. Irritable bowel syndrome. [internet]. Rochester (MN): Mayo Foundation for Medical Education and Research (MFMER); 2014 Jul 31 [accessed 2014 Sep 26]. [12 p]. Available: http://www.mayoclinic.org/diseases-conditions/irritable-bowel-syndrome/basics/definition/CON-20024578.

43. Grundmann O, Yoon SL. Irritable bowel syndrome: epidemiology, diagnosis and treatment: an update for health-care practitioners. J Gastroenterol Hepatol. 2010 Apr;25:691-9. Also available: http://dx.doi.org/10.1111/j.1440-1746.2009.06120.x. PMID: 20074154.

44. McKenzie YA, Alder A, Anderson W, et al. British Dietetic Association evidence-based guidelines for the dietary management of irritable bowel syndrome in adults. J Hum Nutr Diet. 2012 Jun;25:260-74. Also available: http://dx.doi.org/10.1111/j.1365-277X.2012.01242.x. PMID: 22489905.

45. Weinberg DS, Smalley W, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014 Nov;147(5):1146-8. Also available: http://dx.doi.org/10.1053/j.gastro.2014.09.001. PMID: 25224526.

46. Expert Commenter 343. (External, Clinical). Horizon Scanning Structured Comment Form. HS690 - Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome. 2015 Mar 19 [review date].

47. Expert Commenter 403. (ECRI Institute, Health Devices). Horizon Scanning Structured Comment Form. HS690 - Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome. 2015 Mar 6 [review date].

48. Expert Commenter 421. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS690 - Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome. 2015 Mar 5 [review date].

49. Expert Commenter 950. (External, Clinical). Horizon Scanning Structured Comment Form. HS690 - Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome. 2015 Mar 23 [review date].

50. Expert Commenter 1170. (ECRI Institute, Applied Solutions Group). Horizon Scanning Structured Comment Form. HS690 - Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome. 2015 Mar 13 [review date].

51. Expert Commenter 1197. (ECRI Institute, Technology Assessment). Horizon Scanning Structured Comment Form. HS690 - Rifaximin (Xifaxan) for treatment of nonconstipating irritable bowel syndrome. 2015 Mar 13 [review date].